Targeting phosphodiesterase type 4 for improving cognitive fronto-striatal functioning

Chapter 8

Summary

The aim of the current PhD dissertation was to target phosphodiesterase type 4 for improving cognitive fronto-striatal functioning via a translational approach. The general introduction (**Chapter 1**) described the rationale of this dissertation and the aims of the studies discussed herein.

Chapter 2: PDE inhibitors enhance cAMP and/or cGMP signaling via reducing the degradation of these cyclic nucleotides. Both cAMP and cGMP signaling are essential for a variety of cellular functions and exert their effects both pre- and post-synaptically. Either of these second messengers relays and amplifies incoming signals at receptors on the cell surface making them important elements in signal transduction cascades and essential in cellular signaling in a variety of cell functions including neurotransmitter release and neuroprotection. Consequently, these processes can be influenced by PDE inhibitors as they increase cAMP and/or cGMP concentrations. PDE inhibitors have been considered as possible therapeutic agents to treat impaired cognitive function linked to fronto-striatal circuits, including ADHD, schizophrenia and Parkinson's disease. In Chapter 2 we discussed the involvement of PDEs on four related domains: attention, information filtering (sensory- and sensorimotor gating) and response inhibition. Currently, these are emerging cognitive domains in the field of PDE research. We discussed experimental studies and the potential beneficial effects of PDE inhibitors on these cognitive domains. Overall, PDE4 seems to be the most promising target for all domains discussed in the chapter.

Chapter 3: Chapter 3 provides a detailed discussion of the relation between PDEs and dopamine in relation to the cognitive functions. Subsequently, an overview is provided of the current clinical status. Clinical trials investigating the effects of PDE inhibitors in neuropsychiatric disorders are overall very sparse and the wealth of positive preclinical data could not yet be translated into clinical efficacy.

Chapter 4: Research has shown that the process of sensory gating is disrupted in patients suffering from clinical disorders including ADHD, schizophrenia and Alzheimer's disease. PDE inhibitors have received an increased interest as a tool to improve cognitive performance related to fronto-striatal functioning in both animals and man. One of the cognitive areas investigated is sensory gating. Therefore, we investigated the effects of the PDE4 inhibitor roflumilast in a sensory gating paradigm in 20 healthy young human volunteers (age range 18 – 30 years). We applied a placebo-controlled randomized cross-over design and tested 3 doses (100, 300, 1000 µg). Results discussed in this chapter showed that roflumilast improved sensory gating in healthy young human volunteers only at the 100 µg dose. This means roflumilast shows a beneficial effect on gating at a dose that had no adverse effects reported following single-dose administration. This indicates that roflumilast 100 µg

has a favorable side-effect profile. Roflumilast and PDE4 inhibition in general could therefore be seen as a promising treatment in disorders affected by disrupted sensory gating.

Chapter 5: In Chapter 5 we examined the functional output of the fronto-striatal circuit to the thalamus at an electrophysiological level by studying the distinctive effects of PDE4 inhibition on the three basal ganglia pathways: the hyperdirect, direct and indirect pathway. Effects of roflumilast on the three pathways were studied via the tri-phasic (excitation-inhibition-excitation) response of the SNr after infralimbic cortex stimulation. Results show for the first time that stimulation of the infralimbic cortex leads to a tri-phasic response in the SNr, topographically and functionally associated with the cognitive parts of the basal ganglia. Interestingly, we found that PDE4 inhibition resulted in inhibition of the direct pathway and reduced activation of the indirect pathway at the level of the SNr. This finding is likely due to the complexity of the system already at hand at the level of the SNr, i.e. the abundant number of feedback and feedforward connections within the circuits as well as their mediation and modulation by PDE4 and several neurotransmitter systems. Most importantly, in line with previous studies, PDE4 inhibition by roflumilast affects both the direct pathway as well as the indirect pathway of which the latter appears more affected than the former.

Chapter 6: In Chapter 6, the mediating role of PDE4 in the dopaminergic modulation of premature responding (motor impulsivity) was studied. We investigated the effects of roflumilast on premature responding in the choice serial reaction time task (CSRTT) in a hypo, normal and hyper dopaminergic state of the cognitive fronto-striatal circuit. Results showed that both increasing and decreasing dopamine levels resulted in an increase in premature responding in the CSRTT. Results indicated a role for PDE4 inhibitors in shifting performance on premature responding to the right on the U-shaped dose response curve. As a result, it would be interesting to test the effects of PDE4 inhibition in disorders affected by disrupted impulse control related to fronto-striatal hypodopaminergia including ADHD.